● PRINTER RUSH ●

(PTO ASSISTANCE)

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☒ SPEC	7-9-03	

[RUSH] **MESSAGE:**

Pages 26, 33, 36, 37 have illegible data.

Please supply clean specification

Thank you

[XRUSH] **RESPONSE:**

INITIALS:

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REV 10/04

If the modified amino acids, poly amino acids, or peptides are to be converted into microspheres, the mixture is optionally heated to a temperature ranging between about 20 and about 50°C, preferably about 40°C, until the modified amino acid(s) dissolve. The final solution contains between from about 1 mg and to about 2000 mg of compound, poly amino acid, or peptide per mL of solution, preferably between about 1 and about 500 mg per mL. The concentration of active agent in the final solution varies and is dependent on the required dosage for treatment. When necessary, the exact concentration can be determined by for example, reverse phrases HPLC analysis.

When the compounds, poly amino acids, or peptides are used to prepare microspheres, another useful procedure is as follows: Compounds, poly amino acids, or peptides are dissolved in deionized water at a concentration ranging between about 75 and about 200 mg/ml, preferably about 100 mg/ml at a temperature between about 25°C and about 60°C, preferably abbut 40°C. Particulate matter remaining in the solution may be removed by conventional means such as filtration.

Thereafter, the compound, poly amino acid, or peptide solution, maintained at a temperature of about 40°C, is mixed 1:1 (V/V) with an aqueous acid solution (also at about 40°C) having an acid concentration ranging between about 0.05 N and about 2 N, preferably about 1.7 N. The resulting mixture is further incubated at 40°C for a period of time effective for microsphere formation, as observed by light microscopy. In practicing this invention, the preferred order of additions is to add the compound, poly amino acid, or peptide solution to the aqueous acid solution.

Suitable acids for microsphere formation include any acid which does not

(a) adversely effect the modified amino acids, poly amino acids, or peptides *e.g.*, initiate or propagate chemical decomposition;

(b) interfere with microsphere formation;

(c) interfere with microsphere incorporation of the active agent cargo; and

Compound I: ^{1}H NMR (300MHz, D_2O): δ 1.5 (2H, m) 2.0 (2H, t) 2.3 (2H,t) 7.5 (2H, t) 7.6 (1H, m) 7.3 (2H, m)

Compound II: ^{1}H NMR (300MHz, D_2O): δ 1.4 (8H, m) 1.7 (6H, m) 2.1 (2H,t) 1.25 (1H, m) 3.05 (2H, t)

Compound III: ^{1}H NMR (300MHz, DMSO-d_6): δ 0.7 (3H, m) 0.9 (2H, m) 1.1 (3H,q) 1.6 (5H, m) 1.75 (2H, q) 2.1 (2H, t) 3.0 (2H, q) 7.9 (1H,m)

Compound IV: Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.9, H, 5.87, N, 6.27 Found: C, 58.89, H, 5.85, N, 6.07. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.8 (2H, m) 2.3 (2H, t) 3.1 (2H,q) 6.9 (2H, t) 7.4 (1H, t) 7.8 (1H, d) 8.85 (1H, t) 12.0 (1H, s) 12.15 (1H, s)

Compound VI: ^{1}H NMR (300MHz, D_2O): δ 0.8 (2H, m) 1.1 (4H, m) 1.4 (2H,q) 1.6 (7H, m) 2.15 (4H, m) 3.1 (2H, t)

Compound IX: ^{1}H NMR (300MHz, DMSO-d_6): δ 0.9 (q, 3H) 1.2 (m, 7H), 1.3 (q, 2H), 1.5 (q, 3H), 1.9 (q, 2H), 2.0 (d, 1H), 2.2 (t, 2H), 3.0 (q, 3H), 7.7 (s, 1H)

Compound X: ^{1}H NMR (300MHz, DMSO-d_6): δ 0.7(d, 2H), 0.9 (dd, 1H), 1.2-1.3 (m, 7H), 1.5 (q, 3H), 1.6-1.8 (m, 5H), 2.15 (t, 2H), 3.0 (m, 3H), 7.5 (s, 1H), 12.0 (s, 1H)

Compound XXXIII: ^{1}H NMR (300MHz, DMSO-d_6): δ 1.2 (a, 2H), 1.3 (q,2H), 1.3 (q, 2H), 1.5 (q, 2H), 2.2 (t, 2H), 3.0 (q, 2H), 3.5 (s, 2H), 7.3 (m, 5H), 8.0 (s, 1H)

Compound XXXIV: Anal. Calcd for $C_{12}H_{17}NO_4$: C, 62.23, H, 6.83, N, 5.57 Found: C, 61.93, H, 6.80, N, 5.56. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.24-1.34 (m,2H) 1.49 1.57 (m, 4H) 2.19 (t, 2H) 3.26 (qt, 2H), 6.68 (t, 2H), 7.37 (s, 1H), 7.83 (d, 1H) 8.81 (t, 1H), 12.08 (s, 1H), 12.72 (s, 1H)

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Example 1A

An alternate synthesis of compound XIX was as follows:

A 5 L three-neck round bottom flask was fitted with a heating mantle, an overhead mechanical stirrer, an addition funnel, and a thermometer. The reaction was performed under an argon atmosphere. Hydroxylamine-*O*-sulfonic acid (196.7 g, 1.74 moles, 1.10 equiv.) and formic acid (1 L) were charged into the round bottom flask and stirred to form a white slurry. A solution of cyclooctanone (200.0 g 1.58 moles, 1.0 equiv.) in formic acid (600 mL) was added dropwise to the white slurry via the addition funnel. After the addition, the addition funnel was replaced by a reflux condenser, and the reaction was heated to reflux (internal temperature about 105°C) for 1 hour to give a brown solution. After the solution was cooled to room temperature, it was poured into a mixture of saturated aqueous ammonium chloride (1.5 L) and water (1.5 L). The aqueous mixture was extracted with chloroform (3 x 1200 mL). The combined chloroform layers were transferred into a beaker, and saturated sodium bicarbonate (2 L) was added slowly. The chloroform layer was then separated, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to afford a brown oil. The oil was placed in a 500 mL round bottom flask with a

magnetic stirrer. The round bottom flask was placed in a silicon oil bath and was fitted with a short path vacuum distillation head equipped with a thermometer. A Cow-type receiver was connected to three 250 mL flasks. 2-Azacyclononanone (145 g, 65%, mp 64-69°C) was obtained by vacuum distillation (fraction with head temperature range from 80 to 120°C at pressures between 3.0 and 3.4 mmHg).

A 5 L three-neck round bottom flask was fitted with a heating mantle, an overhead mechanical stirrer, a reflux condenser, and a 29 thermometer. A suspension of 2-~~azacyclononanone~~ azacyclononanone (83 g, 0.59 moles, 1.0 equiv.) in 5 M aqueous sodium hydroxide (650 mL, 3.23 moles, 5.5 equiv.) was charged into the round bottom flask. The mixture was heated to reflux (internal temperature about 110°C) for 4 hours to yield a clear yellow solution. The heating mantle and reflux condenser were removed. After the solution cooled to room temperature, it was diluted with water (650 mL) and cooled further in an ice bath. Finely ground *O*-acetylsalicyloyl chloride (114.7 g, 0.59 moles, 1.0 equiv.) was added portionwise to the solution with stirring and continued cooling over 1 hour. After an additional 30 minutes, the ice-bath was removed and stirring was continued at ambient temperature for 21 hours to give a brownish yellow solution. The stirred mixture was acidified with 2 M sulfuric acid (about 850 mL) to a pH of about 1, and a yellow solid was formed. The solid was collected by filtration and was dissolved in warm methanol (1.7 L). Activated charcoal (about 5 g) was added to the methanol, and the solution was stirred for 10 minutes. The activated charcoal was removed by filtration, and the charcoal residue was washed with additional 300 mL methanol. Water (2 L) was added to the combined filtrates (*i.e.* the 2 L methanol), and an off-white solid precipitated upon standing at 4°C overnight. The crude product was filtered and was recrystallized from 65% methanol/water (v/v) to yield Compound XIX (69.1 g, 42%) as off-white solid.

Properties are listed below:

mp 116-117°C; HPLC, ^{1}H NMR and Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.02. Found: C, 64.26; H, 7.81; N, 4.93.